6.0 ANIMAL PATHOLOGY AND PHYSIOLOGY

6.1 THE EVIDENCE

Tables 6.1.1–6.1.20 summarize the literature reviewed for this evaluation in addition to what was reviewed by the NIEHS Working Group. The DHS scientists re-reviewed certain critical studies in the light of newer studies.

The pro and con arguments are presented in Tables 6.2.1-6.2.18.

Summary Tables for In Vivo Bioeffects Review: California EMF Program

TABLE 6.1.1 CHEMICALLY INITIATED BREAST CANCER IN RATS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Beniashvili et al., 1991)	young female rats; groups of 50	20 μT (?); 50 Hz	For either 0.5 or 3.0 hrs per day for up to 158 days; some groups received nitrosomethyl urea (NMU) as a single *i.v.* injection of 50 mg/kg	palpation of tumors & histology	Exposure to a 50 Hz MF increases incidence of mammary gland tumors, decreases latent period for tumor development, & increases incidence of malignant tumors.
(Loscher et al., 1993)	young female Sprague-Dawley (SD) rats; groups of 99	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	Magnetic field (MF) exposure promotes chemically initiated mammary tumorgenicity.
(Mevissen et al., 1993)	young female SD rats; groups of 36 or 99	exposed = 30 μT, sham = 0.7μT& control = ambient; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	The authors offer the tentative conclusion that MF exposure can act as a promoter or co-promoter of breast cancer.
(Loscher et al., 1994)	young female SD rats; groups of 36 or 99	exposed = 30 μT, sham = 0.7μT & control = ambient; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors & histology	Under the conditions examined, MF exposure does not promote chemically initiated mammary tumorgenicity.
(Baum et al., 1995)	young female SD rats; groups of 99	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	histology data for exp't of Loscher et al. (Loscher et al., 1993)	MF exposure did not increase incidence but did accelerate tumor development.
(Loscher et al., 1994)	female SD rats; 36 or 99 per group	sham-exposed, 0.7 μT, 10 μT, 50 μT, or 100 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	# tumor data from several previous exp'ts; not based on histology	There is a strong, linear dose-response relationship.

TABLE 6.1.1 DMBA & BREAST CANCER IN RATS (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Mevissen et al., 1996a)	female SD rats; 99 per group	exposed = 10 μT; shams = 0.01μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	The authors do not emphasize lack of differences between groups in this exp't. They concentrate on lack of melatonin effects in this exp't & increased tumors in other exp'ts.
(Mevissen et al., 1996b)	female SD rats; 99 per group	exposed = 50 μT; shams = 0.05μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	palpation of tumors only; no histology	Exposure to 50 μT exerts a clearly detectable, dose-dependent co-promotional effect on DMBA-initiated tumorgenicity without affecting melatonin.
(Anisimov, Popovich & Zabezhinski, 1997)	outbred female rats, groups of 20 - 50	not well described; 50 Hz, 160 A/m in coils of box solenoids	presumably c. 24 hrs/day for up to c. 1 year; some groups received 50 mg/kg NMU; groups held in 24-hr light, 24-hr dark or 12:12 light:dark	tumors by palpation, plus histopathology	MF increases breast cancer: light increases & dark inhibits breast cancer.
(Loscher, Mevissen & Haussler, 1997)	young female SD rats; 99 per group	exposed = 100 μT & sham-exposed = 0.1 μT; 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	# tumors; data from previous exp'ts	MF promotional effect is affected by season of year.
(Ekstrom, Mild & Homberg, 1998)	young female SD rats; groups of 60	exposed = 0.25 & 0.5 mT; 50 Hz	c. 20 hrs/day for 25 wks; MF was "intermittent" (15 sec on & 15 sec off); DMBA = 7 mg	tumors assessed by palpation; no histology	MF exposure had no promotional effect on tumor development.
(Mevissen et al., 1998)	young female SD rats; 99 per group	exposed = 100 μT & sham-exposed = 0.1 μT; 50 Hz, horizontal sham-exposed & 100 μT; 50 Hz	c. 24 hrs/day for 13 wks; DMBA = 20 mg	tumors assessed by palpation & visualized at autopsy but no histopathology	Exposure to 100 μT had a clear promotional effect on tumor development, replicating a previous observation.
(Anderson et al., 1999)	young female SD rats; 100 per group	sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz, 100 μT @ 60 Hz	18.5 hrs/day for 13 wks; DMBA = 20 mg	# tumors palpated, plus histology	This exp't provides no evidence that MF exposure promotes tumor or carcinoma development.
		sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz			

TABLE 6.1.1 DMBA & BREAST CANCER IN RATS (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Boorman et al., 1999a)	young female SD rats; 100 per group	sham-exposed, 100 μT @ 50 Hz, 500 μT @ 50 Hz, 100 μT @ 60 Hz	18.5 hrs/day for 26 wks; DMBA = 10 mg	# tumors, etc.; complete histology	No evidence that MF exposure promotes tumor development.
(Thun-Battersby, Mevissen & Loscher, 1999)	young female SD rats; groups of 99	sham exposed & 100 μT; 50 Hz, horizontal	c. 24 hrs/day for 27 wks; DMBA = 10 mg	% tumors @ 13 wks & % tumors @ autopsy; histology completed	The data indicate that MF exposure promotes tumor development.

TABLE 6.1.2 LEUKEMIA OR LYMPHOMA

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Reif, Lower & Ogilvie, 1995)	pet dogs	MF measured in yard & house	epidemiology study of real-world exposure	cases = dogs with lymphoma & controls = dogs with other forms of cancer	As with humans, there is a weak association between lymphoma & MF exposure.
(Fam & Mikhail, 1996)	CFW mice; exposed = 92 & control = 41	25 μT @ 60 Hz; controls at 0.5 μT; horizontal	continuous for 3 generations; natural light plus 12:12 L:D	premalignant, early lymphoma or advanced lymphoma in 3rd generation	Multi-generation exposure to very strong MF induces lymphoma.
(McCormick et al., 1998)	PIM mice; 30 per group	sham-exposed (0.1 μT), 2 μT, 20 μT, 0.1 μT (contin.) or 0.1 μT (on/off); 60 Hz, linearly polarized, transient-free	18.5 hrs/day for 23 wks; ENU-initiated	lymphoma incidence & latency	MF does not induce cancer in genetically susceptible mice.
	TSG-p53 mice; 30 per group	sham-exposed or 1 mT (contin.)	18.5 hrs/day for 23 wks; genetically "initiated"		
(Morris et al., 1999)	male Fischer 344 rats; 108 per group, 18 animals assessed at 5, 6, 7, 8, 9, & 11 wks	sham-exposed 2 μT @ 60 Hz 1 μT @ 60 Hz horizontal	20 hrs/day; all subjects were LGL-initiated; one group received ^{60}Co @ 5 Gy	hematology, spleen growth, & LGL infiltration of liver & spleen	MF exposure does not promote leukemia in rats.

TABLE 6.1.3 SKIN CANCER

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kumlin et al., 1998a)	female transgenic (K2) mice & non-transgenic littermates; four groups of 43 or 44	shams = < 0.05 μT, continuous = 100 μT, intermittent = 1.3, 13 & 130 μT for 20 min each, followed by "0" for 2 hrs; 50 Hz	exposure was for 10.5 months; UV light at 1 MED given 3 times/wk	tumor incidence	MF exposure modestly increased tumor development.
(Sasser et al., 1998)	SENCAR mice; 56 per group	sham-exposed 2 mT @ 60 Hz	6 hrs/day for 5 days/wk for 23 wks	% with tumors # tumors per animal	MF exposure does not initiate cancer.

TABLE 6.1.4 BRAIN CANCER

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Mandeville et al., 2000)	female F344 rats; 50 per group; 8 groups, including 2 internal controls & 1 positive control	sham (< 0.02 μT), 2, 20, 200 or 2,000 μT; 60 Hz	20 hrs/day for 420 days; animals received *in utero* exposure to NMU; positive control group received TPA	histology for tumors in central & peripheral portions of nervous system	MF exposure does not promote NMU-initiated brain tumors.

TABLE 6.1.5 LONG-TERM TOXICOLOGY BIOASSAYS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Boorman et al., 1999b)	female & male Fischer 344 rats; 100 per group	sham-exposed, 2 μT, 200 μT, 1 μT (contin.), or 1 μT (1 hr on/off); 60 Hz, horizontal	18.5 hrs/day for 2 years	histology of all tissues	Lifetime MF exposure does not cause toxicity, including cancer. Thyroid C-cell adenomas & carcinomas regarded as an anomaly.
(McCormick et al., 1999)	female & male B6C3F1 mice; 100 per group	sham-exposed, 2 μT, 200 μT, 1 μT (continuous), or 1 μT (1 hr on/off); 60 Hz, linearly polarized, transient free	18.5 hrs/day for 2 years	histology of all tissues	Lifetime MF exposure does not cause toxicity, including cancer.

TABLE 6.1.6 REPRODUCTION & DEVELOPMENT

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kubinyi et al., 1998)	pregnant CFLP mice; progeny followed to postnatal day 24; 240 adult females & 240 adult males exposed	100 μT, 50 Hz, vertical	exposed on days 2-18 of gestation for 7 hrs per day; adults exposed for 17 days	survival plus body & organ weights	MF exposure does not affect these measures.
(Svedenstal & Johanson, 1998)	young male CBA/Ca mice; 2 groups of 12 (6 wks of age at start) & 2 groups of 6 (4 wks of age at start)	sham exposed = ambient (0.1 - 0.7 μT); MF-exposed = 5 μT; 50 Hz	54 hrs	^{125}IUdR incorporation; counts for whole body & for 12 specific organs	MF exposure does not affect cell proliferation.
(Ryan et al., 1998)	male & female SD rats; 40 per group	sham-exposed, 2 μT, 200 μT, 1 μT (continuous), or 1 μT (1 hr on & 1 hr off); linearly polarized, transient free, 60 Hz	18.5 hrs/day; F_0 exposed for 18 wks; & F_1 exposed for 29 days	many measures in F_0, F_1, & F_2 generations	MF exposure does not cause reproductive or developmental effects.

TABLE 6.1.7 HEMATOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Bonhomme-Faivre, Mace & Bezie, 1998b)	Swiss mice; 6 wks of age at start; 2 groups of 12	monthly average = 5 μT & diurnal cycle = 3.2-6.8 μT; controls with ambient MF (< 0.1 μT)	exposed for 350 days in cages on floor in a laboratory directly above the main service bus bars of a 13 kV transformer	many hematological measures sampled at 20, 43, 63, 90, & 350 days	E/MF exposure produces diverse hematologic changes that differ with duration of exposure.
(Burchard, Nguyen & Block, 1999)	Holstein cows; multiparous, non-lactating (n = 8); & ovariectomized heifers (n = 7)	10 kV/m & 30 μT; 60Hz, vertical EF & horizontal MF	exposure was for 30 days for c. 22 hrs/day; data were collected during pre-exposure & post-exposure periods; indwelling catheters were used to sample cerebrospinal fluid	concentrations of 9 ions in both plasma & cerebrospinal fluid	MF exposure produced changes in concentrations of five ions.
(Svedenstal & Johanson, 1998)	CBA/S mice; males & females used in 1st exp't; males used in remaining 4 exp'ts; animals usually 20-30 days of age at start, except exp't 2 animals = 84 days of age	exposed = 5 μT (rms, 14 μT peak-peak) & controls = 0.7-9.1 μT; 50 Hz	in 5 exp'ts, exposure was for various durations; exp't 1 = 240 days, exp't 2 = 140 days, exp't 3 = 60 days, exp't 4 = 96 hrs, exp't 5 = 90 days	numbers & types of leukocytes & erythrocytes	MF exposure does not exert strong effects on erythrocyte & leukocyte formation.

TABLE 6.1.8 IMMUNOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Haussler et al., 1999)	young, female SD rats; data from groups of 5-9	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	sham- or MF-exposed for 14 wks, following 20 mg DMBA treatment; c. 24 hrs/day	IL-1 & IL-2 expression	MF exposure does not affect IL-meditated stimulation of lymphocytes *ex vivo*.
			sham- or MF-exposed for 1 day, 1 wk or 2 wks; c. 24 hrs/day		
(Komeva et al., 1999)	adult male CBA mice; 3 groups of 100	22 μT, 50 Hz	1 hr/day for 5 days; measurements made 1, 24 or 96 hrs after end of MF exposure	thymus weight & numbers of colony-forming units in spleen & bone marrow	Exposure to 50 Hz MF can affect natural defense mechanisms of the body.
			marrow from MF exposed animals injected into mice previously exposed to lethal dose of X-rays (9 Gy)		
(Thun-Battersby, Westermann & Loscher, 1999)	young female SD rats; groups of 6 - 8	exposed = 100 μT & shams = 0.1 μT; 50 Hz, horizontal	3 days, 14 days, or 13 wks; c. 24 hrs/day	many common measures of B & T lymphocyte type & function	MF exposure does not affect the mechanisms involved in control of lymphocyte homeostasis.

TABLE 6.1.9 BONE GROWTH

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL COMMENTS
(Landry et al., 1997)	young male Fischer rats; six groups of 30	exposed = 100 μT & shams = < 1 μT; 60 Hz	continuous for 24 or 72 hrs	osteoblast concentration, distance between proliferating cells, & % callus in defect	Bone growth is enhanced by 60 Hz MF; effect is on differentiation rather than proliferation.
(Vera, Picazo & Royuela, 1999)	OF1 mouse; second generation exposed to sexual maturity; four groups of 30	exposed = 15 μT & unexposed animals "exposed to only geomagnetic fields in the room", 50 Hz, horizontal	continuous, *in utero* to 12 (females) or 14 wks (males) of age	26 densitometric & mechanical variables	MF exposure does not significantly affect measures of bone growth.

TABLE 6.1.10 STRESS PROTEINS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(DiCarlo, Farrell & Litovitz, 1998)	chicken embryo (developmental stage 24); 451 control, 66 heat-shocked, & 506 MF-exposed	sham (< 0.5 μT), 4, 6, 8 or 10 μT; 60 Hz; all MF-exposed data were combined	20 min of MF exposure @ 37.8^{0}C; another group was heated to 43^{0}C for 20 min without MF exposure; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Acute MF exposure increases survival & this is a simple model to demonstrate MF bioeffects.
(DiCarlo & Litovitz, 1999)	White Leghorn chicken embryos (developmental stage 24) from two flocks; n per condition = 63 - 148	sham (< 0.5 μT) or 8 μT, 60 Hz	expose for 20 - 120 min; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Genetic differences can modify an MF-induced biologic effect.
(DiCarlo, Farrell & Litovitz, 1999)	chicken embryo (developmental stage 24); 957 eggs used in 80 exp'ts	sham (< 0.5 μT), 8 μT, & 8 μT + "noise" MF; 60 Hz	two MF groups for 20 min @ 37.8^{0}C; plus sham control group, plus 4th group heated to 43^{0}C for 20 min; produce anoxia & then observe survival	% survival during a variable-duration period after a variable-duration period of anoxia	Addition of a noncoherent MF cancels the effect of a coherent MF.

TABLE 6.1.11 ORNITHINE DECARBOXYLASE ACTIVITY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kumlin et al., 1998a)	female transgenic (K2) mice & non-transgenic littermates; four groups of 43 or 44	shams = < 0.05 μT, continuous = 100 μT, intermittent = 1.3, 13 & 130 μT for 20 min each, followed by "0" for 2 hrs; 50 Hz, vertical	exposure was for 10.5 months; UV light at 1 MED 3 times/wk	ODC activity at end of chronic exp't (in which increased skin cancer had occurred)	MF exposure produced no measurable effects on ODC activity.
(Kumlin et al., 1998b)	female K2 mice; 4 groups of 15	100 μT, 50 Hz, vertical; continuous or intermittent (1.3, 13, 130 & 0 μT), plus sham-exposed	duration = 10.5 months; UV only, UV + continuous MF, & UV + intermittent MF	ODC activity plus putrescine, spermidine, & spermine concentrations of skin	No ODC effects apparent at end of chronic exp't.
	female K2 mice; 3 groups of 12	100 μT, 50 Hz, vertical; sham, continuous MF, & intermittent MF	as above; but only 24 hrs of exposure		Acute MF exposure affects epidermal polyamine synthesis; putrescine is elevated & ODC activity is down-regulated.
(Svedenstal & Johanson, 1998)	male CBA mice; one exp't (4 wks of age) with 12 exposed & 12 control, & a 2nd exp't (6 wks of age) with 6 exposed & 6 control	exposed = 5 μT & shams = 0.1 - 0.7 μT; 50 Hz, vertical	continuous exposure for 54 hrs	cell proliferation measured with radiolabeled (^{125}I) deoxyuridine in 11 organs & whole body	Cell proliferation was not affected by MF exposure.

TABLE 6.1.11 ORNITHINE DECARBOXYLASE ACTIVITY (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(DiGiovanni et al., 1999)	SENCAR mice; 24 subjects per each of 8 groups; for statistical comparisons, n = 3 or 4 per group	sham-exposed ("minimal stray" MF) or 2 mT; 60 Hz	6 hrs/day for 5 days/wk; DMBA-initiated & TPA-promoted animals were assessed at 1, 2 & 5 wks; TPA doses = 0, 0.85, 1.70 or 3.40 nmol.	epidermal thickness & labeling, ODC activity, & protein kinase C activity	MF exposure does not promote measured biomarkers of skin cancer.
(Mevissen, Haussler & Loscher, 1999)	female SD rats; 50 - 52 days of age at start of exp't; in 3 exp'ts, groups sizes were 6 to 12	exposed = 100 μT & shams = 0.1 μT (stray MF); 50 Hz, horizontal	exposure for c. 22 hrs/day for periods of 1, 2, 8, or 13 wks; two near-replicate exp'ts were completed; a 3rd exp't subdivided the thoracic mammary complex into cranial & middle portions	ODC activity in mammary glands	Increases in ODC were observed after 2 wks of exposure, especially in cranial complex.

TABLE 6.1.12 ENZYME ACTIVITY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Kubinyi et al., 1998)	pregnant CFLP mice; progeny followed to postnatal day 24; adult males also studied; 240 female & 240 males	exposed = 100 μT; 50 Hz, vertical; controls not clearly described	exposed on days 2-18 of gestation for 7 hrs per day; thus adults exposed for 17 days	activity of enzyme tRNA synthetase in brain & liver or adults & weanlings	Males showed slightly reduced activity in liver & females showed slightly increased activity in brain.
(Kula et al., 1998)	rats	18 μT, 50 Hz	8 hrs/day for 8 wks	activities of 4 connective tissue enzymes	Metabolism of connective tissue enzymes is affected by MF exposure.
(Singh, Khanduja & Mittal, 1998)	mice	2 or 10 μT @ 50 Hz	**Have not received a copy of the paper.**	activity of a total of 5 enzymes, some phase I & some phase II enzymes	Phase I enzyme activity is increased, leading to reduced glutathione concentrations.
(Singh, Kaur & Khanduja, 1999)	6 young male Swiss mice	50 Hz, 2 μT	8 hrs/day for 8 wks; data from wks 0, 4, 6, & 8	respiratory excretion of $^{14}CO_2$ from radiolabeled nitrosodiethylamine	Enhanced enzyme activity occurs, which could be a protective response.
(Singh et al., 1999)	young male Swiss mice; 3 groups of 6	sham, 2 μT & 10 μT; 50 Hz	8 hrs/day for 8 wks	activities of 4 antioxidant defense enzymes in red blood cells, liver & lung; plus lipid peroxidation in liver & lung	Antioxidant defense enzymes are stimulated by MF exposure; effects are most apparent at 2 μT suggesting an amplitude "window."

TABLE 6.1.13 OTHER ENDPOINTS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Picazo et al., 1995a)	female OF1 mice at 14 wks of age; 2 groups of 30	15 μT, 50 Hz, horizontal; MF conditions for controls not described	2nd generation with "chronic" exposure	water content, atomic absorption (Ca, Mg, Ni, Zn & Fe) or emission (Na & K) spectrophotometry & descriptive histology	Calcium content was decreased in MF-exposed animals. Variations in fiber morphology, similar to those common in myopathies or early dystrophies, occurred in exposed animals.
(Hurych et al., 1996)	male Wistar rat; groups of 9 or 10 for biochemistry & cytology; groups of 5 for histology	10 μT, 50 Hz; MF conditions for controls not described	1 hr/day, 5 days/wk for 4 months; animals also received weekly pulmonary exposure to fibrogenic & nuisance dusts & to $CdCl_2$	analysis of bronchoalveolar lavage fluid & lung tissue	MF exposure does not damage cell membranes but does decrease collagen synthesis in response to fibrogenic particles.
(Rencova, Jerabek & Volf, 1997)	young-adult female Wistar rats; 7 per group	10 μT @ 50 Hz; "parallel vector"; control condition not described	5 different exp'ts were completed	retention of ^{210}Po or ^{234}Th in nine tissues	Numerous differences occurred between MF-exposed & control groups. Results appear to depend upon experimental conditions & isotope.

TABLE 6.1.14 MELATONIN

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Anisimov et al., 1997)	outbred female rats; groups of 20 to 50	box solenoids at 160 A/m; 50 Hz	presumably c. 24 hrs/day for up to 390 days; some groups received 50 mg/kg NMU; groups held in 24-hr light, 24-hr dark or 12:12 light:dark	serum melatonin	MF exposure does not appear to greatly affect melatonin. Light affects melatonin & NMU reduces melatonin.
(Burchard, Nguyen & Block, 1998a)	lactating Holstein cows; n = 16	horizontal 30 μT & vertical 10 kV/m; 60 Hz	within-subject, counter-balanced (ABA & BAB) exposures for three 28-day periods	plasma melatonin concentrations in samples collected every 0.5 hour for 14 hrs	MF exposure does not affect nocturnal melatonin concentration.
(Loscher, Mevissen & Lerchl, 1998)	young female SD rats; group sizes c. 10	100 μT, 50 Hz, horizontal	7 exp'ts: exposures of 1 day, & 1, 2, 4, 8, & 13 wks, with some internal replication efforts	plasma melatonin concentration at 3, 4, 5, &/or 6 hrs after onset of darkness	Exposure to 50 Hz MF does not reliably reduce melatonin.
(Mevissen et al., 1998)	female SD rats; 99 per group	sham-exposed (0.1 μT) & MF-exposed (100 μT); 50 Hz, horizontal	c. 24 hrs/day for 13 wks; DMBA = 20 mg	serum melatonin after 12 wks of exposure	MF exposure does not reduce melatonin in this exp't; reasons for inconsistency in MF effects on melatonin are not known.
(Picazo et al., 1998)	40 male OF1 mice assessed at sexual maturity (3 months)	control & 15 μT, 50 Hz	continuous exposure into 3rd generation	plasma melatonin concentrations	Cumulative MF exposure causes loss of diurnal melatonin rhythm.
(Reiter, 1998)	SD rat	sham (< 0.2 μT) & 100 μT; 60 Hz	9 exp'ts with exposures of 15 or 60 min, single exp'ts with 3, 4, or 6 hrs of exposure; 5 exp'ts with 12 hrs of exposure	pineal & blood melatonin concentrations; NAT activity	MF exposure does not affect melatonin.

TABLE 6.1.14 MELATONIN (CONT.)

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Bakos et al., 1999)	male Wistar rats; groups of 5 or 6	exposed = 100 μT & controls = 1 μT; 50 Hz, horizontal, parallel or perpendicular to magnetic north	MF exposure for 24 hrs on 3rd day of 5-day exp't	urinary excretion of 6-sulphatoxymelatonin	MF exposure under these conditions does not affect melatonin.
(Heikkinen, Kumlin & Laitenen, 1999)	female CBA/S mice; 526 days of age; groups of 24	50 Hz, vertical, regularly varying (20 min at 1.3, 13 & 130 μT); shams were kept in an unenergized coil	24 hrs/day for 1.5 years	urinary melatonin excretion	At the end of near-lifetime MF exposure, there were no effects on melatonin.
(Selmaoui & Touitou, 1999)	young (9 wks) & old (23 months) male Wistar rats; groups of 6	Exposed = 100 μT (50 Hz) & controls = ambient	18 hrs/day for 1 wk	pineal melatonin plus SNAT & HIOMT activity	MF exposure reduced melatonin in young rats but not in older rats.
(Wilson, Matt & Morris, 1999)	Siberian (Djungarian) hamsters; males (4 - 6 months); group sizes = c. 20 animals	0.1 mT (most exp'ts) or 0.5 mT (one exp't); shams < 0.1μT; 60 Hz, horizontal	four different exp'ts; 15 min to 42 days of exposure; short- & long-day conditions	pineal melatonin	60 Hz MF reduce melatonin.

TABLE 6.1.15 OTHER HORMONES

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Picazo et al., 1995b)	female of1 mice; 2nd exposed generation	control & 15 μT; 50 Hz	apparently continuous	quantitative light microscopy & descriptive electron microscopy	No statistically significant differences, but 30% of exposed animals showed signs of adrenal hyperfunction.
(Romo et al., 1997)	female mice	control & 15 μT; 50 Hz	apparently continuous	adrenal gland	Presumably effects were found.
(Bonhomme-Faivre et al., 1998b)	Swiss mice; 6 wks of age at start; 2 groups of 12	monthly average = 5 μT; diurnal cycle = 3.2-6.8 μT. Controls, housed in another room, had ambient MF < 0.1 μT; 50 Hz	exposed for 350 days in cages on floor in a laboratory directly above the main service bus bars & of a 13 kV transformer	cortisol measured at 90 & 190 days	Cortisol concentrations were reduced at 190 days.
(Burchard, Nguyen & Block, 1998b)	Holstein cows, 16 non-pregnant & lactating	10 kV/m vertical & 30 μT horizontal; 60 Hz	using a counter-balanced design, exposure was for either 1 or 2 estrous cycles, which were 24-27 days in duration; exposure was for c. 21 hrs/day	plasma progesterone, including area under the curve	Plasma progesterone (mean & AUC) did not differ significantly with exposure, but estrous cycle length was increased by 15% during MF exposure.
(Wilson et al., 1999)	Siberian (Djungarian) hamsters; males (4-6 months), group sizes c. 20	exposed = 0.5 μT (one exp't) or 0.1 μT (most exp'ts); shams < 0.1 μT; 60 Hz, horizontal	4 different exp'ts; 15 min to 42 days of exposure; short- & long-day conditions	Plasma prolactin, body, & organ weights	MF exposure can affect neuroendocrine system.

TABLE 6.1.16 BEHAVIOR

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 mT, 50 Hz; methods are not described	1 hour, twice weekly for 3 months; intra-tracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	functional observation battery including over 30 endpoints	MF exposure affects various behavioral measures.
(Sienkiewicz, Haylock & Saunders, 1998)	adult male C57BL/6J mice; groups of 6 - 8	exposed = 7.5 μT, 75 μT, 0.75 μT, or 7.5 μT @ 50 Hz; sham-exposed c 50 μT	45 min of exposure immediately before daily behavioral testing for 10 days	level of performance (% correct) in 10 daily training sessions in an 8-arm radial maze	Exposure immediately before testing reduced acquisition in the 0.75 & 7.5 μT groups.
		exposed = 0.75 μT @ 50 Hz; sham-exposed = < 50 μT	45 min of exposure ending 45 min before daily behavioral testing for 10 days		With a delay of 45 min, MF exposure had no effect on acquisition.
		exposed = 7.5 μT, 75 μT, or 0.75 μT @ 50 Hz; sham-exposed 50 μT	45 min of exposure after daily behavioral testing for 10 days		Exposure following daily sessions produced no effects on acquisition.
(Stern & Laties, 1998)	mature Long-Evans rats; 3 female & 4 male	homogeneous, vertical 60 Hz EF of 100 kV/m	49 EF operant sessions of 50 min; 103 other sessions involved light exposure; & c. 150 other sessions involved no potentially aversive stimulus	ratio of responses on two levers, one turning the stimulus "off" & one turning it "on"	The time spent responding on the lever associated with EF- or light- onset was reduced 5-10%; similar to light, EF exposure can be weakly aversive.

TABLE 6.1.17 NEUROTRANSMITTERS & OPIODS

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Burchard et al., 1998c)	Holstein cows; n = 8	10 kV/m vertical & 30 μT horizontal; 60 Hz	pre-exposure, exposure, & post-exposure periods 30 days in duration	concentrations of seven neurotransmitter-related metabolites in cerebrospinal fluid	Quinolinic acid increased, suggesting EMF exposure produced a weakening of the blood brain barrier.
(Kavaliers, Wiebe & Ossenkopp, 1998)	young CF1 male mice; groups of 10	exposed = horizontal, 141 μT (peak, not rms), shams = ambient MF (< 0.4 μT peak); 60 Hz	inject with analgesia-producing drug, expose for 30 min, & conduct hot plate test	analgesia, measured as latency to licking of foot	MF exposure reduces analgesia.
			inject with analgesia-producing, inject with Ca-channel blocking drug, expose for 30 min, & conduct hot plate test		MF exposure reduces analgesia; calcium channel blocks the effect.

TABLE 6.1.18 NEUROCHEMISTRY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 μT, 50 Hz; exposure methods are not described	1 hour, twice weekly for 3 months; intra-tracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	Mn content of brain, lungs, liver, & kidney	MF exposure increased brain Mn content.
(Lai & Carino, 1998)	adult male SD rats; 8 groups of 6-8	2 mT & sham exposed (14 μT); 60 Hz	expose for 1 hour & assay; pre-treat with vehicle or 1 of 2 opiate receptor agonists	sodium-dependent high-affinity choline uptake in frontal cortex & hippocampus	MF exposure reduces uptake, but both drugs blocked the effect.
(Lai & Carino, 1999)	adult male SD rats; 8 groups of 7-16	0.01, 0.1, 0.5, 1.0, 1.5 or 2.0 mT; 60 Hz; sham-exposed controls in "bucked" (canceled) coils	30, 45, 60, or 90 min	cholinergic activity (high affinity choline uptake) in frontal cortex & hippocampus	Immediately after exposure, cholinergic activity in two brain regions is reduced; there is a interaction of flux density & exposure time.
(Singh & Lai, 1998)	adult male SD rats; n = 8 per treatment condition	exposed = 0.5 mT & sham-exposed controls in "bucked" coils	expose for 2 hrs & wait 4 hrs	single strand breaks in brain cells by comet assay	Acute MF exposure damages DNA of brain cells, probably through free radical processes.

TABLE 6.1.19 ELECTROPHYSIOLOGY

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSIONS
(Vojtisek et al., 1996)	adult female Wistar rats: untreated control group = 12, sham-exposed group = 12, MF exposed group = 16	10 μT, 50 Hz; exposure methods are not described	1 hour, twice weekly for 3 months; intratracheal administration with manganese solution; no MF & no Mn group, Mn & no MF group, & MF + Mn group	visual evoked potentials (P1 latency)	MF exposure did not significantly affect VEP latency.
(Potschka, Thun-Battersby & Loscher, 1998)	young adult female Wistar rats; 1 group of 9	sham-exposed at ambient (0.03 - 0.04 μT) when MF- exposed group at 1 μT; sham exposed at 0.1 μT when MF-exposed at 100 μT; 50 Hz, horizontal	acute exp't involved 1 hour at 1 μT, 1 hr at 100 μT, & 2 hr at 100 μT; rats were fully kindled before MF exposure	brain stimulation, through electrodes implanted in the amygdala, was used to study kindling & seizures; several parameters measured on multiple occasions	Acute exposure had no effect on any of 4 parameters.
	young adult female Wistar rats; 2 groups of 10		exposed at 1 μT for 1 wk followed by 100 μT for 7 wks; MF or sham exposure for c. 22 hrs/day		Chronic exposure to MF exerts a weak inhibitory effects on three seizure parameters.
(Vorobyov et al., 1998)	male Wistar rats; 5 exp'ts, usually with 3 rats per exp't	48 Hz, 21 μT & 0 Hz, 21 μT (3rd harmonic for calcium cyclotron resonance)	pre-exposure, exposure & post-exposure periods, each 30 min in duration; also morphine treatments given	38 measures of EEG power, expressed as percent change from previous condition	Weak MF can influence spontaneous electrical brain activity.

TABLE 6.1.20 INVERTEBRATES

REFERENCE	ANIMAL	FIELD CHARACTERISTICS	EXPOSURE CONDITIONS	ENDPOINTS	PAPER'S GENERAL CONCLUSION
(Jenrow, Smith & Liboff, 1995)	*Dugesia tigrina* (planaria); no fewer than 8 replicate exp'ts; minimum n = 192	1, 10, 40, 51 or 78 μT; 60 Hz, horizontal	23 hrs/day for 12 days	% abnormal following period for regeneration of severed head	MF exposure causes abnormal development in regenerating planaria.
(Hemmersbach, Becker & Stockem, 1997)	three species of ciliates, including wild-type & mutant *Paramecium* (with abnormal calcium channels)	2 μT, 50 Hz	30 min	swimming speed & linearity measured with image-processing software	MF exposure alters swimming, increasing speed & reducing linearity, by affecting cell membrane transport mechanisms for calcium.
(Kavaliers, Choleris & Prato, 1998)	land snail (*Cepaea nemoralis*); groups of 10	141 μT (peak); 60 Hz, horizontal; sham-exposed in coils without current	15 min exposure; an enkephalinase inhibitor was used; nitric oxide mechanisms were investigated using agonist & antagonist	antinociception measured as latency of foot withdrawal on hotplate	The inhibitory effects of MF exposure on opiod analgesia involve nitric oxide.
(Kikuchi et al., 1998)	fruit fly (*Drosophila melanogaster*)	0.5 μT or 5 μT; controls < 1 μT; 50 Hz, horizontal	lifetime for 40 generations	genetic indices of mildly deleterious & lethal mutations, plus viability decreasing rate	MF exposure at very high MF flux density is not mutagenic.
(Tipping et al., 1999)	3rd instar fruit fly (*Drosophila melanogaster*) larvae; triplicate assays from 100 mg	larvae reared in either "ambient" or shielded (0.004 μT) conditions; MF was 8 μT, 50 Hz	half received 20-min MF exposures in the shielded space, & half received shielded exposures	membrane probe binding of three genes, *Cobia*, *Histone 1.9*, & *HSP 70a*	MF-exposure reduced gene transcripts in larvae reared in shielded environment but not in larvae reared in ambient environment.
(Junkersdorf, Bauer & Gutzeit, 2000)	nematode (*C. elegans*); two different transgenic strains were used; one included gene for hsp16, & other included gene for hsp70	0, 50, 100, or 150μT; 50 Hz	60, 120, or 180 min at 29 or 30° C, depending upon strain	lacZ gene used as a reporter: for 1st strain, β-galactosidase staining of the roller phenotype was used; for the 2nd, β-galactosidase activity was measured photometrically	MF exposure enhances the production of heat shock proteins elicited by mild thermal stress.

6.2 PRO AND CON ARGUMENTS

TABLE 6.2.1

RODENT BREAST CANCER PROMOTION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Replications of the hypothesis-generating studies by Losher group were unsuccessful. They were conducted in two independent reputable labs, following good laboratory practice. Any statistically significant association noted suggested a *protective* effect.	(F1) Losher and his group have consistently reported increased tumorigenesis, if not necessarily carcinogenesis, in DMBA treated rats.	(C1) Unsuccessful replications cannot claim to refute the hypothesis-generating study if the protocol and the conditions are different. Losher's results stand unrefuted but also unreplicated.
	(F2) Attempts to replicate them did not follow the Losher protocol. In particular, the rate of tumors in the sham exposed rats (initiated with DMBA from a different supplier) was so high (>90%) as to mask any reasonable increase due to EMF exposure.	
	(F3) The "protective" associations refer to the number and/or size of tumors in diseased animals, not to the percentage of animals who developed tumors, which was not very high in both the exposed and sham group.	

TABLE 6.2.2

LEUKEMIA AND LYMPHOMA		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) A set of chronic exposure experiments showed no effects.	(F1) Experiments conducted using the traditional NTP protocol of testing for chemical carcinogenicity rely on the assumption that the risk resulting from exposure to levels well above those found in the environment carries a proportionally high risk and, therefore, sufficient power can be obtained with small sample sizes.	(C1) A null result of a test which may not be a sensitive indicator of the human carcinogenicity of a complex mixture does not pull down confidence as much as a supportive result would increase confidence.
(A2) If proponents accept the positive Losher results, they cannot argue that a pure sinusoidal 60 Hz wave is not the right exposure parameter to test.	(F2) The epidemiological evidence on EMF exposure suggests no additional risk above levels of 8-10 mG and, therefore, these studies would not have sufficient power.	(C2) If one believes Loscher's positive breast cancer results, one cannot invoke "wrong ingredient" or "insufficient power" arguments.
	(F3) Exposure conditions in the laboratory do not mimic the complex mixture of EMF parameters found in the environment.	(C3) All experiments designed to test for cancer initiation are irrelevant to the present evaluation.

TABLE 6.2.3

SKIN CANCER		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Seven out of ten studies provide no evidence for carcinogenicity.	(F1) See leukemia discussion.	(C1) See leukemia discussion.

TABLE 6.2.4

LONG-TERM CARCINOGEN BIOASSAYS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Three 1-2 year bioassay experiments conducted according to "the gold standard" of NTP procedures developed during decades of testing for chemical carcinogenicity showed no support for the hypothesis.	(F1) One study showed equivocal results at one tumor site (C-cell adenomas and carcinomas of the thyroid in male rats). The author regarded this study as "equivocal."	(C1) See leukemia discussion.
(A2) If proponents accept the positive Losher breast cancer results, they cannot argue that other carcinogenicity bioassays do not have sufficient statistical power.	(F2) Animal bioassays have not always detected human carcinogens at first (cigarette smoke, asbestos, arsenic, and benzene are examples).	
	(F3) Exposure to EMF without prior initiation cannot test the most commonly held belief that EMFs are not initiators, but act at later stages of cancer.	
	(F4) The Losher breast cancer studies were promotion studies: the animals were initiated with a chemical carcinogen while in the standard toxicology tests they are not. Therefore, the statistical power requirements are quite different.	

TABLE 6.2.5

LIVER CANCER		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Two studies of chemically initiated liver cancer revealed no effect of EMF exposure.	(F1) See leukemia discussion.	(C1) See leukemia discussion.

TABLE 6.2.6

REPRODUCTION AND DEVELOPMENT		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Eight studies on mammals (rodents) showed no effect on embryo development.	(F1) One study on hamsters reported changes in spermatogenetic cell populations.	(C1) Although the reproductive effects on chicken embryos are not considered relevant to humans by regulatory toxicology, and although not sufficiently "robust" for regulatory purposes, they help overcome the belief, based on the theoretical models, that no effect can take place at these levels (50-100 mG).
(A2) The effects on chicken embryos are not relevant to humans.	(F2) Several studies on chicken embryos show consistent effects with one strain of chicken. The importance of these studies is twofold: (F2a) Even if not relevant to produce reproductive effects in mammals, they show that EMF may have biological effects in living organisms, negating the prediction of theoretical models and the claim that *in vitro* results are due to artifacts. (F2b) It highlights how susceptible these experiments are to parameter choice (in this case chicken strain).	(C2) The evidence of differential response by different strains of chicken opens the possibility of species differences in susceptibility to EMF effects.
(A3) The null mammal results take precedence.		(C3) The null mammalian results could be due to species differences, but this evidence decreases confidence somewhat.
(A4) The effects on chicken embryos are not robust in that they are not larger than fluctuations between control groups in different laboratories and, though statistically significant in several laboratories, should be ignored.		(C4) If one believes the chicken results, one cannot invoke "wrong ingredient" or "insufficient power" arguments.
(A5) Chicken embryo studies did not evaluate results at a sufficiently stable and advanced stage.	(F5) The chicken results increase confidence somewhat.	

TABLE 6.2.7

PHYSIOLOGY – HEMATOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The pattern of results is consistent with no effect.	(F1) Although the pattern of results is not statistically significant, most of the major studies (5 out of 8) showed an effect on red cell, white cell, or ion concentrations in blood. Therefore the evidence, if not convincing, is suggestive of an effect.	(C1) Given the multiple parameters investigated, the likelihood of this pattern of results by chance is larger than the likelihood if EMFs caused a particular effect.
		(C2) The failure to affect a physiological parameter does not much sway confidence in a pathological effect.

TABLE 6.2.8

IMMUNOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The pattern of results is consistent with no effect.	(F1) The majority of studies (6 out of 8) report an effect. Even when the analysis is restricted to the more recent studies, there is no consistent negative outcome.	(C1) The results are inconclusive.

TABLE 6.2.9

BONE REPAIR		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is evidence that EMF is effective in accelerating bone repair, but the intensities used are well above those of interest in the context of environmental exposure. The exact mechanism is not understood.		(C1) This is not a health hazard and is not evaluated here.

TABLE 6.2.10

STRESS PROTEINS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) All data come from the same group. There is no clear dose response. The effects are largely limited to one strain of chicken embryos.	(F1) These data provide easily verifiable evidence that EMF exposure, at levels below those for which well-understood mechanisms can be invoked, induce stress response. The fact that the effect is strain sensitive is consistent with the finding of the hen-house type experiments.	(C1) These results advance a viable mechanistic theory involving the concepts of a minimum sensing interval and signal coherence. However, at present, they are not sufficiently established to have more than a weak positive effect on the degree of confidence.

TABLE 6.2.11

ENZYME ACTIVITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear evidence of an effect in vivo. All positive results are from exposure to very strong fields. The direction of the effect (decreased ODC activity) is opposite to increased activity reported in vivo.		(C1) Once again, this strain of evidence is not a very sensitive indicator of pathology. The reviewers cannot rule out that predominantly negative results are not due to the choice of experimental conditions.

TABLE 6.2.12

MELATONIN		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The literature is evenly divided between studies reporting an effect and those that do not.	(F1) The experiments failing to show an effect do not explain away the results of those which do. On the other hand, there are many possible explanations for the negative results. Several of the positive findings were obtained with low-level exposures, below the threshold predicted by theoretical models.	(C1) Although it would be desirable to deal with a more consistent body of evidence, there is sufficient unrefuted evidence of an effect. However, whether or not this is related to a pathological endpoint is unclear.
		(C2) The fact that these effects have been reported at levels where theoreticians predicted that no effect should be observed is a strong reason to doubt these theoretical models and the argument that these fields, even if perceived, are too weak to produce noticeable effects.

TABLE 6.2.13

OTHER HORMONES		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no clear relationship between the weak effects reported and pathological endpoints.	(F1) Most studies show an effect. Endocrine dysfunctions are known to be causally related to several types of cancer and other health effects.	(C1) Overall, the results provide moderate evidence that EMFs affect the endocrine system *in vivo*, although most of these were obtained at exposure levels higher than those found in the environment (although below the theoretical thresholds).

TABLE 6.2.14

NEUROPHYSIOLOGY – BEHAVIOR		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Consistent evidence of effects on the operation of the central nervous systems at levels only moderately above environmental ones.	(C1) Although often overlooked and not strongly indicative of a hazard, this is the most consistent set of experimental data.

TABLE 6.2.15

NEUROTRANSMITTERS AND OPIOIDS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Consistent evidence of an effect.	(C1) Effects reported at the mT level, 1,000 times higher than the highest environmental fields.

TABLE 6.2.16

NEUROCHEMISTRY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) No clear relation to cancer and other adverse health effects.	(F1) Three recent studies concur in showing that EMF exposure induces changes in brain function.	(C1) CNS effects might have pathological implications, but link is unclear.
(A2) Effects reported in the high microtesla range, well above environmental levels.		

TABLE 6.2.17

ELECTROPHYSIOLOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Effects reported at a level much higher than the highest environmental fields.	(F1) There is a small, but persuasive body of literature indicating that power-frequency EMFs interact acutely with the CNS to produce functional changes.	(C1) CNS effects might have pathological implications, but link is unclear.
(A2) Some effects are arguably beneficial, rather than hazardous.		
(A3) Other studies report no effects or scattered effects, possibly resulting from multiple comparisons.		

TABLE 6.2.18

6.38 INVERTEBRATES		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Strong MF were not found to be mutagenic in fruit flies exposed for 40 generations.	(F1) The hypothesis is that MF are a risk factor for cancer, a multifactorial disease. Proving that they are not the initiator does not weaken the hypothesis.	
(A2) These are mostly older studies without a specific hypothesis to test.	(F2) Other studies report a variety of adverse effects on invertebrates.	

6.3 CONCLUSIONS

Overall, the animal studies can be divided into three categories: 1) those showing no effect and having statistical power to show one; 2) those that do not significantly weaken the hypothesis because there are many possible explanations for a negative result, including lack of statistical power and use of inappropriate exposure metrics and modalities; 3) those showing an effect at mT levels, which may be important for future research, but is not relevant to the present evaluation.

Those showing an effect at near-environmental levels argue against accepting the theoretical models predicting a very high threshold for any effect to occur. These increase the reviewers level of confidence in a causal association, irrespective of whether or not the effect is obviously related to cancer. Included in this category are the data on neurological effects, the chicken embryo studies, and the Losher mammary tumor results.

Given the significant differences in the conduct of these mammary tumor replication studies (Anderson et al., 2000), compared to the original research (most notably the different and very high rate of cancer in the control group, possibly traceable to the use of different suppliers for the initiator and animals), the reviewers cannot place much weight on the failure to replicate these studies until they understand the explanation of the different results (Anderson, Kelman & Weigel, 1987).

Overall, the animal pathology studies are predominantly, but not entirely, negative. However, in the case of the EMF mixture the reviewers believe that, given the many difficulties of experimental design and conduct of animal pathology studies, that a pattern of many false-negative results was quite possible, even if the effect were to be real. This is because of the problems of choosing the right species to test, the special problem of power as judged from the expected dose response from the epidemiology, and the issue of choosing the right aspect of the mixture to test. Reviewers 1 and 3 had their confidence increased slightly by the mammary tumor and chicken evidence. Reviewer 2 was not moved one way or the other, but felt that the chicken studies and mammary tumor studies needed to be pursued toward clarification.